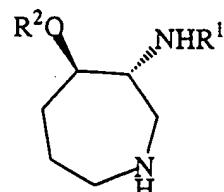


Claims

what is claimed is:

A process for the manufacture of compounds of the formula

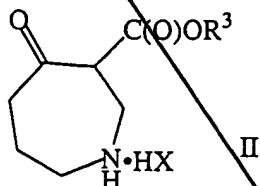


II

wherein R¹ and R² are independently an acyl residue of an aromatic carboxylic acid,

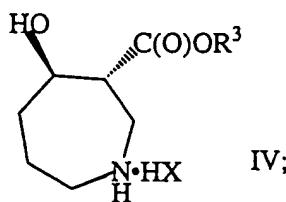
10 comprising:

a) asymmetrically hydrogenating a compound of the formula



15

wherein R^3 is lower-alkyl,
to a compound of the formula

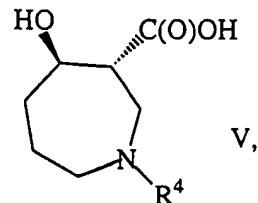


IV.

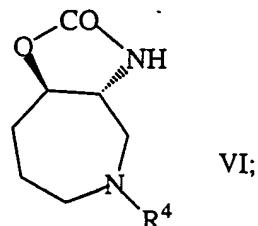
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b) providing a protecting group to the compound of formula IV.

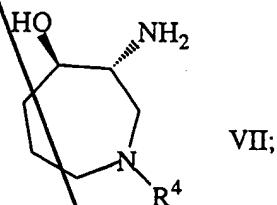
c) saponifying the compound of formula IV after step b), forming a compound of the formula



d) converting the compound of formula V into a compound of the formula

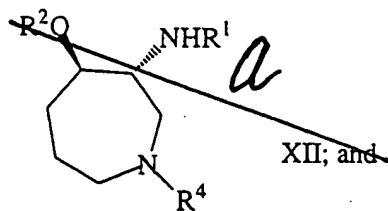


e) hydrolyzing the compound of formula VI into a compound of the formula



f) N- and, respectively, O-acylating the compound of formula VII with an aromatic carboxylic acid of the formula R¹COOH or R²COOH

20 to form a compound of the formula



g) cleaving off protective groups on the compound of formula XII, to form the compound of formula I.

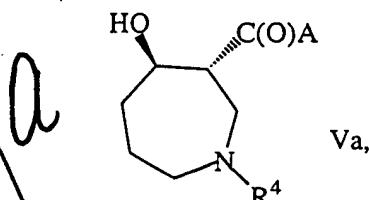
5

2. The process of claim 1, wherein R¹ and R² are p-hydroxybenzoyl.

10

3. The process of claim 1, further comprising in step c

10
i) converting the compound of formula V into a compound of the formula



15

wherein A is azido or amino; and

ii) performing a Curtius or Hofmann degradation on the compound of formula Va to yield the compound of formula VI.

20

4. The process of claim 1, wherein the compound of formula II is hydrogenated in the presence of a rhodium-diphosphine complex catalyst having a formula selected from the formulae

25

$(RuL)^2+(X^0)_2$	III-a
$(RuLX^2)^2+(X^0)_2$	III-b
$(RuLX^1X^2)+X^3$	III-c
$RuL(X^4)_2$	III-d

and

wherein

X⁰ is selected from the group consisting of BF₄⁻, ClO₄⁻,
B(phenyl)4⁻, SbF₆⁻, PF₆⁻ and Z¹-SO₃⁻;

5 X¹ is halide;

X² is benzene, hexamethylbenzene or p-cymene;

X³ is selected from the group consisting of halide, ClO₄⁻,
B(phenyl)4⁻, SbF₆⁻, PF₆⁻, Z¹-SO₃⁻ and BF₄⁻;

X⁴ is selected from the group consisting of Z²-COO⁻, Z³-
SO₃⁻, allyl and CH₃COCH=C(CH₃)O-;

10 Z¹ is halogenated lower alkyl or halogenated
phenyl;

Z² is selected from the group consisting of lower alkyl,
phenyl, halogenated lower alkyl and halogenated
phenyl;

15 Z³ is lower alkyl or phenyl; and

L is an optically active atropiso-meric, diphosphine ligand.

5. The process of claim 4, wherein L is selected from the
group consisting of

20 MeOBIPHEP (6,6'-Dimethoxybiphenyl-2,2'-diyl)bis-
(diphenylphosphine);

BIPHEMP (6,6'-Dimethylbiphenyl-2,2'-diyl)bis-
(diphenylphosphine);

25 BINAP [(1,1'-Binaphthyl)-2,2'-diyl]bis-
(diphenylphosphine);

pTol-BIPHEMP (6,6'-Dimethylbiphenyl-2,2'-diyl)bis(di-
(p-tolyl)phosphine);

pAn-MeOBIPHEP 6,6'-Dimethoxy-P,P,P',P'-tetrakis-(4-
30 methoxy-phenyl)-biphenyl-2,2'-bis-
phosphine;

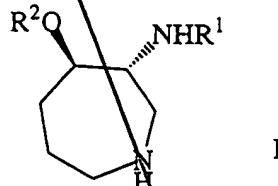
pDMA-MeOBIPHEP 6,6'-Dimethoxy-P,P,P',P'-tetrakis-(4-
dimethylamino-phenyl)-biphenyl-2,2'-
bis-phosphine;

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	p Phenyl-MeOBIPHEP	(6,6'-Dimethoxybiphenyl-2,2'-diyl)-bis(bis-(biphenyl)-phosphine);
	mTol-BIPHEMP	(6,6'-Dimethylbiphenyl-2,2'-diyl)bis(di-(m-tolyl)phosphine);
5	Cy ₂ -MeOBIPHEP	P ₂ ,P ₂ -Dicyclohexyl-6,6'-dimethoxy-P ₂ ',P ₂ '-diphenyl-biphenyl-2,2'-bis-phosphine;
	2-Furyl ₂ -BIPHEMP	P,P-Diphenyl-P',P'-di-2-furyl-(6,6'-dimethyl-biphenyl-2,2'-diyl)diphosphine;
10		
	(3,5-Me,4-MeO)-MeOBIPHEP	6,6'-Dimethoxy-P,P,P',P'-tetrakis-(dimethyl-4-methoxy-phenyl)-biphenyl-2,2'-bis-phosphine;
15	DiMeOBIPHEP	(5,5',6,6'-Tetramethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine);
	TriMeOBIPHEP	(4,4',5,5',6,6'-Hexamethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine); and
	2-Furyl-MeOBIPHEP	(6,6'-Dimethoxybiphenyl-2,2'-diyl)bis(di-2-furylphosphine).
20		

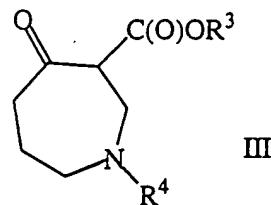
6. The process of claim 5, wherein the catalyst is
Ru(OAc)₂(R)-MeOBIPHEP.

7. A process for the manufacture of compounds of the
25 formula



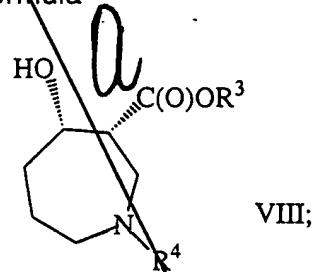
Wherein R¹ and R² are independently an acyl residue of an aromatic carboxylic acid, comprising:

5 a) microbially reducing a compound of the formula

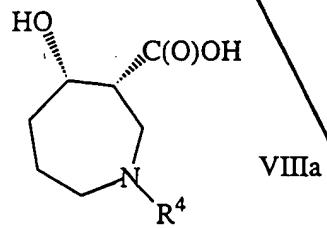


wherein R³ is lower-alkyl and R⁴ is a protecting group,

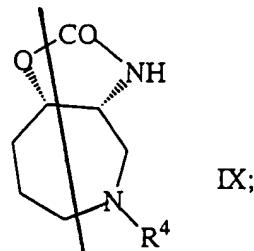
10 to a compound of the formula



15 b) saponifying the compound of formula VIII to a compound of the formula



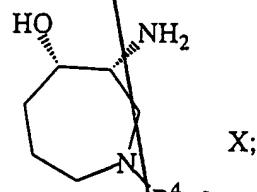
20 c) transforming the compound of formula VIIIa into a compound of the formula



IX;

d) hydrolyzing the compound of formula IX into a compound of the formula

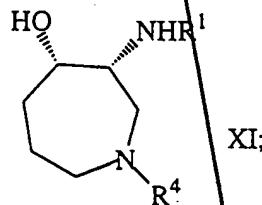
5



X;

e) acylating the compound of formula X with an aromatic carboxylic acid of the formula R^1COOH to a compound of the formula

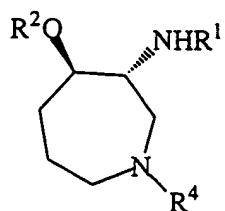
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XI;

f) acylating the compound of formula XI with an aromatic carboxylic acid or a reactive derivative thereof, to form a compound

15 of the formula



XII; and

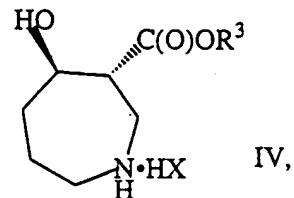
g) cleaving off the protecting group R^4 from the compound of
20 formula XII yielding the compound of formula I

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8. The process of claim 7, wherein the compound of formula ~~III~~ is reduced using a culture of ~~Hanseniaspora uvarum~~ R 1052.

5 9. The process of claim 7, wherein R¹ and R² are p-hydroxybenzoyl.

a
Reekh
B1
10 10. The compounds of the formula

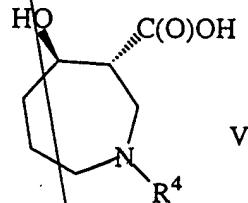


10

wherein R³ is lower alkyl.

11. The compound of claim 10, ethyl (3R,4R)-4-hydroxy-15 azepan-carboxylate hydrochloride.

A
12. The compound of the formula



20

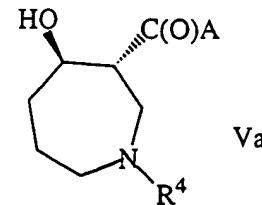
wherein R⁴ is a protecting group.

13. The compound of claim 12, (3R,4R)-4-Hydroxy-azepan-1,3-dicarboxylic acid 1-tert.-butyl ester.

25

a

14. ^A The compound of the formula

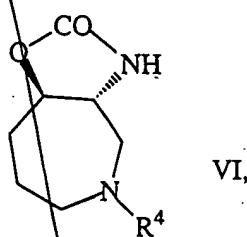


^B
cont

5 wherein A is azido or amino and R⁴ is a protecting group.

a

15. ^A The compound of the formula



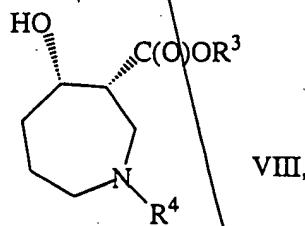
10

wherein R⁴ is a protecting group.

16. The compound of claim 15, (3aR,8aR)-5-tert-Butoxycarbonyl-2-oxo-octahydro-oxazolo(4,b-c)azepine.

15

17. ^A The compound of the formula



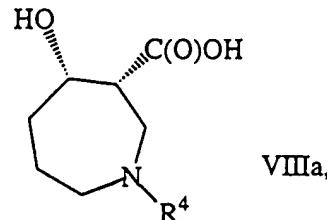
20

wherein R³ is lower alkyl and R⁴ is a protecting group.

18. The compound of claim 17, ethyl (3R,4S)-1-(tert-butoxycarbonyl)-4-hydroxy-azepan-3-carboxylate.

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a 19. The compound of the formula



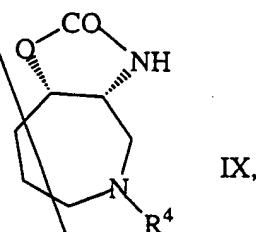
5

wherein R⁴ is a protecting group.

20. The compound of claim 19, (3R,4S)-4-Hydroxy-azepan-1,3-dicarboxylic acid 1-tert-butyl ester.

10

A 21. The compound of the formula



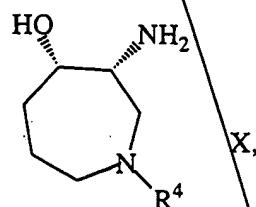
15

wherein R⁴ is a protecting group.

22. The compound of claim 21, tert. Butyl (3aR,8aS)-2-oxo-octahydro-oxazolo(4,b-c)azepine-5-carboxylate.

20

A 23. The compound of the formula



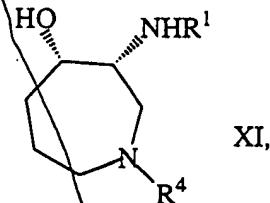
wherein R⁴ is a protecting group.

24. The compound of claim 23, tert-Butyl (3R,4S)-3-amino-4-hydroxy-azepan-1-carboxylate.

5

^A
25. The compound of the formula

a
B
cont



10

26. The compound of claim 25, tert-Butyl (3R,4S)-3-(4-tert-butoxy-benzoylamino)-4-hydroxy-azepan-1-carboxylate.

15

27. The compound tert-Butyl (3R,4R)-3-(4-tert-butoxy-benzoylamino)-4-(4-tert-butoxy-benzoyloxy)-azepan-1-carboxylate.

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